NDA 22-512 Dabigatran

Efficacy Review

Cardio-Renal Advisory Committee Meeting
September 20, 2010

Aliza Thompson, MD, MS

Outline

- Overview of RE-LY's design

- Efficacy findings

- Aspects of study design and conduct affecting interpretation

RE-LY

- Non-inferiority study, open label with respect to warfarin and blinded with respect to two doses of dabigatran (110 and 150 mg BID)

- 18,113 subjects randomized (1:1:1)

- Primary endpoint: stroke and systemic embolism

- Population: non-valvular atrial fibrillation with ≥ 1 risk factor for stroke; warfarin naïve and non-naïve patients (balanced enrollment sought)

Primary endpoint: stroke or systemic embolism (SEE)

	D110 vs. warfarin	D150 vs. warfarin	D150 vs. D110
HR (95% CI) **P-value superiority**	0.90 (0.74, 1.10) 0.29	0.65 (0.52, 0.81) 0.0001	0.72 (0.58, 0.90) 0.004

FDA margin=1.38

3
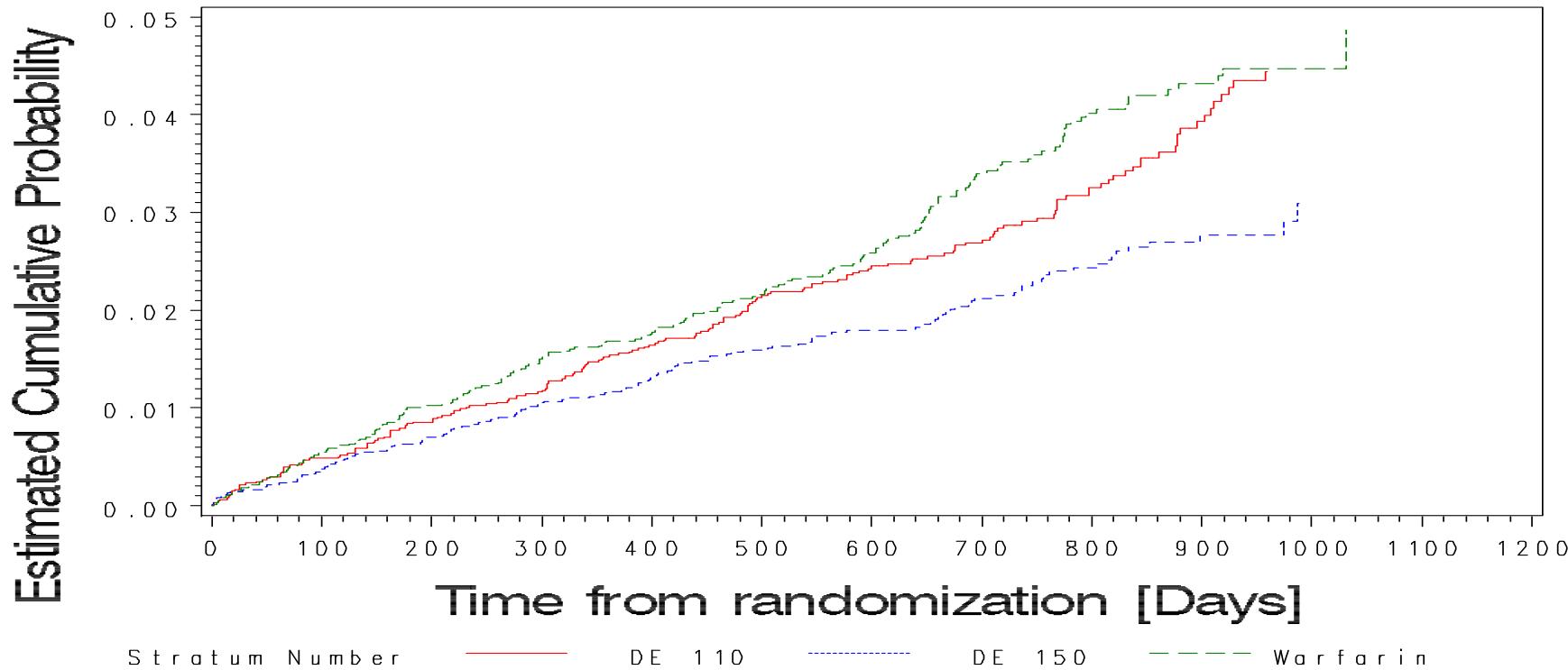
Components of composite

	D110 N=6015	**D150** N=6076	**Warfarin** N=6022
Stroke or SEE	183 (1.5)	134 (1.1)	202 (1.7)
Stroke	171 (1.4)	122 (1.0)	186 (1.6)
Ischemic	152 (1.3)	103 (0.9)	134 (1.1)
Hemorrhagic	14 (0.1)	12 (0.1)	45 (0.4)
SEE	15 (0.1)	13 (0.1)	21 (0.2)

		D110 vs. warfarin	**D150 vs. warfarin**
Components of primary endpoint			
Stroke	HR (95% CI)	0.91 (0.74, 1.12)	0.64 (0.51,0.81)
	p-value	0.38	.0001
SEE	HR (95% CI)	0.71 (0.37,1.38)	0.61 (0.30,1.21)
	p-value	0.31	0.16
Types of strokes			
Ischemic	HR (95% CI)	1.13 (0.89,1.42)	0.75 (0.58,0.97)
	p-value	0.31	0.03
Hemorrhagic	HR (95% CI)	0.31 (0.17,0.56)	0.26 (0.14,0.49)
	p-value	0.0001	<0.0001

4

Other endpoints and MACE

Number of subjects with event and annualized event rates (%)			
	D110 N=6015	**D150** N=6076	**Warfarin** N=6022
PE	14 (0.1)	18 (0.2)	12 (0.1)
MI	87 (0.73)	89 (0.74)	66 (0.56)
Vascular mortality	289 (2.4)	274 (2.3)	317 (2.7)
All cause morality	446 (3.7)	438 (3.6)	487 (4.1)
MACE	403 (3.4)	341 (2.8)	398 (3.4)

MACE			
	D110 vs. warfarin	**D150 vs. warfarin**	**D150 vs. D110**
HR	1.00	0.84	0.83
95% CI	(0.87, 1.15)	(0.73, 0.97)	(0.72, 0.96)
p-value	0.95	0.02	0.01

Interpreting the efficacy findings (relative to warfarin)

Factors to consider:

- *Subject follow up*

- *Adequacy of anticoagulation in the warfarin arm*

- *Potential sources of bias in setting open-label study*

- *Single trial (lack of replication)*

- *Late finalization of statistical analysis plan (end of study close out=March 15, 2009; statistical analysis plan finalized=May 8, 2009)*

Subject Follow Up
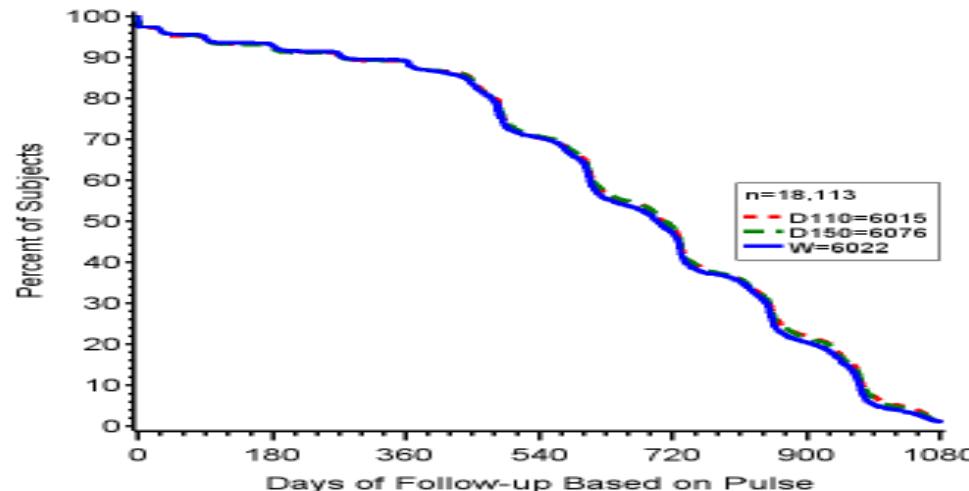
	D110 N=6015	D150 N=6076	Warfarin N=6022
Treated	5983 (99.5)	6059 (99.7)	5998 (99.6)
Completed study	5765 (96.4)	5808 (95.9)	5748 (95.8)
Completed follow up but stopped study medication prematurely	1155 (19.3)	1183 (19.5)	900 (15.0)
Premature discontinuation	218 (3.6)	251 (4.1)	250 (4.2)
Last visit at which subject seen in person> 6 months from study close out*	489 (8.1)	499 (8.2)	469 (7.8)

*Based on recorded vital signs (pulse data) on visit CRF

Stroke incidence: recent RCTs and historical warfarin trials

	Year	Placebo	Warfarin/Vitamin K antagonist
Recent RCTs			
SPORTIF III	2003		2.2
SPORTIF V	2005		1.1
ACTIVE W	2006		1.4
RE-LY	**2009**		**1.6**
Historical primary prevention trials of warfarin*			
AFASAK I	1989	4.8	2.2
SPAF I	1991	7.8	3.0
BAATAF	1990	3.0	0.6
CAFA	1991	3.7	2.5
SPINAF	1992	4.8	1.4
Overall	**1989-1992**	**4.6**	**1.7**
Historical secondary prevention trial of warfarin*			
EAFT	1993	12.3	3.9

*Based on events/patient-years reported in Hart et al. Ann Intern Med 2007; 146: 857-867.

8

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Time in therapeutic range

Time in therapeutic range (TTR) in RE-LY (~64%) perhaps not dissimilar to that seen in some other recent RCTs (~64 to 68%)* but what is optimal?

Reported TTR of >73% for warfarin arm in tecarfarin trial (used a central dose control center and pharmacogenomic information).

*ACTIVE W and SPORTIF trials

Comparisons of TTR across studies are not straightforward

- For a range of reasons, the correlation between TTR and stroke rates is not perfect:

   Similar TTR in SPORTIF III and V (66 and 68%, respectively) and yet different ischemic stroke rates: 1.9% in SPORTIF III and 1.1% in SPORTIF V.

- TTR reflects measured and reported INR values. Depending upon the adequacy of INR monitoring and extent to which subjects assigned to warfarin remain on therapy, TTR may or may not be reflective of the degree of anticoagulation in the warfarin arm.

Exposure to warfarin and monitoring

Exposure to warfarin
- 17.9% of subject permanently discontinued warfarin
- 52% of subjects had an interruption in therapy

INR monitoring
- ~2% of randomized and treated subjects lacked follow up INR data (the majority were on therapy for 30 days or less)
- For subjects with INR measurements that were taken and reported, ~32% had at least 1 measurement taken >60 days from the prior measurement; ~16% with at least 1 taken > 90 days

Percent time in therapeutic range vs. frequency of monitoring
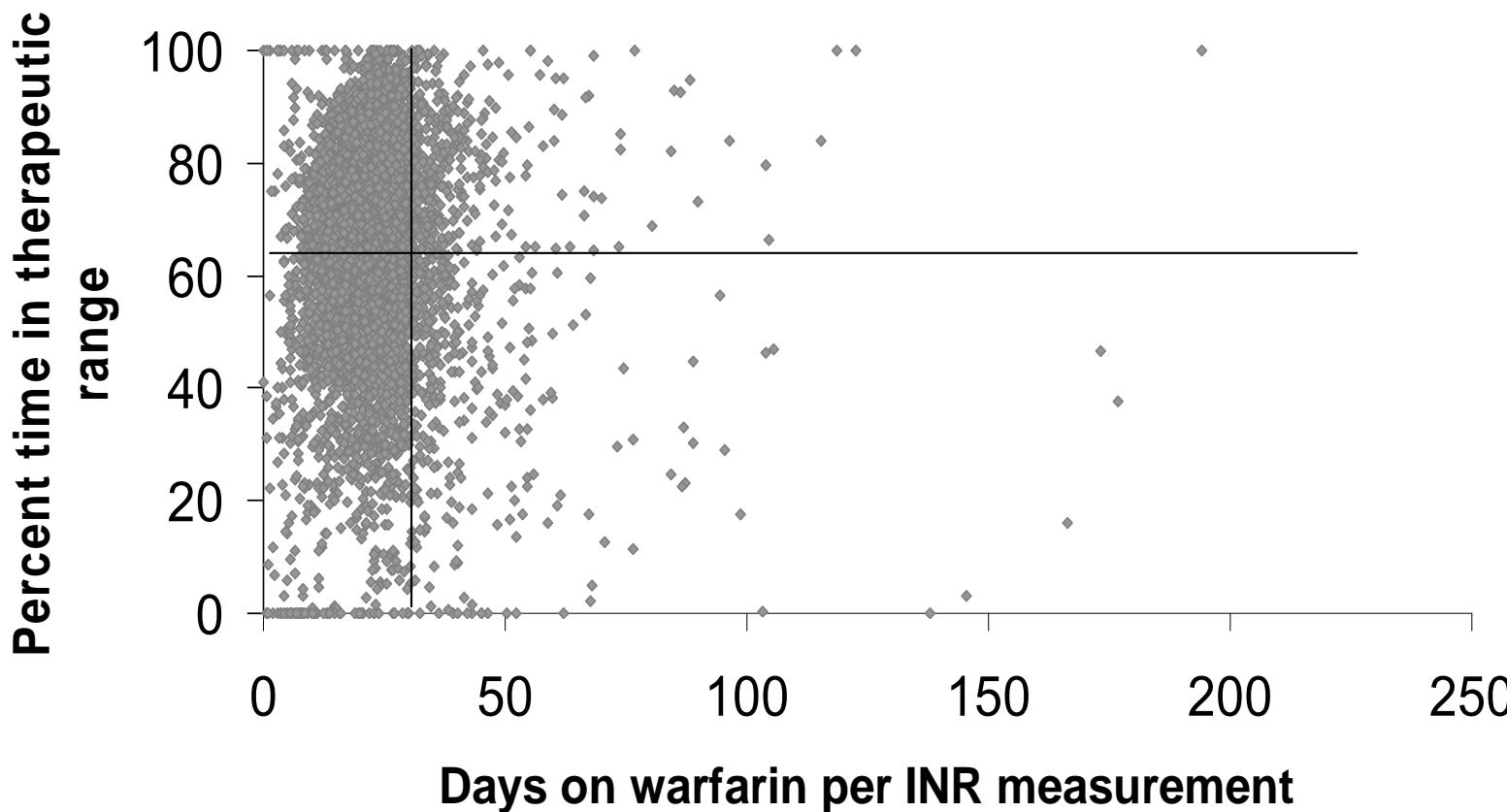
*Days on warfarin are cumulative and not necessarily consecutive. Vertical line drawn at 30 days; horizontal line drawn at 64% time in therapeutic range.

Analyses by level of INR control

	Centers with INR control below the median		Centers with INR control above the median	
	D110 vs. warfarin	D150 vs. warfarin	D110 vs. warfarin	D150 vs. warfarin
Stroke/SEE				
HR	0.86	0.57	0.96	0.77
95% CI	0.66, 1.12	0.42, 0.76	0.71, 1.30	0.56, 1.06
p-value	0.26	0.0002	0.78	0.10
All-cause death				
HR	0.77	0.78	1.08	1.01
95% CI	0.65, 0.92	0.66, 0.93	0.89, 1.30	0.84, 1.23
p-value	0.005	0.007	0.43	0.89

Median time in TTR= 67% for centers

RE-LY as a PROBE study

- The PROBE design: *Prospective, randomized, open-label, blinded endpoint evaluation*

- Sampling of phrases found in documents sent to adjudicators:

    "recruited in RE-LY study…on Dabigatran"

    "atrial fibrillation being treated with warfarin"

    "on warfarin"

    "he is using an experimental blood thinner"

    "Sunday to check INR levels..consult with physician regarding the coumadin dose. Target INR 2.0"

    Other references to INR/checks of INR

Mitigating bias in the ascertainment of endpoint events

Methods used to capture additional potential endpoint events included:

- screening of investigator-reported reasons for hospitalization and adverse events

- questionnaire querying subjects for signs/symptoms of strokes

All require that investigators report a suggestive event in order to capture an event via this method.

Hospitalization CRF: a closer look

4. Reason(s) for Admission: *(Mark [X] all that apply)*

CRF #   Report #

☐ 1. Outcome Event ⟶ *Specify* ⟶ ☐☐☐ - ☐☐

Other Cardiovascular:

☐ 2. New angina   ☐ 3. Atrial fib/flutter ☐ 4. Non fatal cardiac arrest   ☐ 5. Supraventricular arrhyth

☐ 6. Ventricular arrhythmia

Surgery:

☐ 7. Valve surgery   ☐ 8. CABG surgery ☐ 9. PTCA surgery   ☐ 10. Carotid endarterectomy

☐ 11. Peripheral angioplasty/surgery   ☐ 12. Limb amputation

☐ 13. Other surgery _____
Specify

Other Non-Cardiovascular:

☐ 14. Cancer   ☐ 15. Injury (e.g. fall) ☐ 16. Fracture   ☐ 17. Psychiatric

☐ 18. Hematologic (specify below)   ☐ 19. Genito-urinary (specify below)

_____   _____

☐ 20. Gastrointestinal (specify below)   ☐ 21. Other (specify below)

_____   _____

☐ 22. Diabetic complications (specify below)

_____

5. State which of the above was the *primary* reason for hospitalization (enter corresponding number): ☐☐

Signature of Investigator
or Designee: _____   Date: ☐☐☐☐ ☐☐ ☐☐
                                                      year   month   day

16

Permanent interruptions of study medication by main reason

	D110 N=5983	D150 N=6059	Warfarin N=5998
Serious AE not related to outcome event	162 (2.7)	170 (2.8)	119 (2.0)
Didn't want to take study drug	424 (7.1)	459 (7.6)	405 (6.8)
Other	471 (7.9)	507 (8.4)	372 (6.2)
Adverse Event	157 (2.6)	164 (2.7)	72 (1.2)
Lab changes	44 (0.7)	57 (0.9)	17 (0.3)
Procedure, hospitalization, surgery	30 (0.5)	35 (0.6)	46 (0.8)
Other	240 (4.0)	251 (4.1)	237 (4.0)
Outcome event *	261 (4.4)	246 (4.1)	177 (3.0)

* Breakdown shown in next slide; source for data: sponsor's Table 15.1.1:3, submission dated April 19, 2010

Permanent interruptions of study medication by main reason (continued)

Breakdown of "Outcome Events"	D110 N=5983	D150 N=6059	Warfarin N=5998
Primary endpoint or TIA			
Stroke	53 (0.9)	42 (0.7)	26 (0.4)
TIA	20 (0.3)	15 (0.2)	0
SEE	10 (0.2)	1 (0.0)	2 (0.0)
Bleeding			
Major Bleed	53 (0.9)	61 (1.0)	66 (1.1)
Minor bleed	67 (1.1)	76 (1.3)	37 (0.6)
Other			
PE	5 (0.1)	5 (0.1)	1 (0.0)
MI	9 (0.2)	8 (0.1)	8 (0.1)
Death	18 (0.3)	17 (0.3)	18 (0.3)
Not matched with the algorithm	42 (0.7)	37 (0.6)	33 (0.6)

Source for data: sponsor's Table 15.1.1:3, submission dated April 19, 2010

Reviewer's conclusions

- *Analyses support that both doses reduce the incidence of stroke/systemic embolism in patients with non-valvular atrial fibrillation.*

- *Dabigatran 150 mg is more effective than the 110-mg dose.*

- *Anticoagulation in the warfarin arm and trial design/conduct were reasonable but not optimal.*

- *Superiority over warfarin was not established.*

20

Outline

- Major bleeding

- Potential drug induced liver injury (DILI)

- Myocardial infarction (MI)

Bleeding definitions – only need one

Definitions	Major	LT	GUSTO severe[1]	ICH[1]
Bleeding with hemoglobin (g/dL) reduction	≥ 2	**≥ 5**		
Bleeding leading to blood transfusion	2 U	4 U		
Symptomatic bleeding in critical area/organ	✓			
Symptomatic intracranial bleed	✓	✓	✓	✓
Bleeding associated with hypotension requiring intravenous inotropes	✓	✓	✓	
Necessitated surgical intervention	✓	✓	✓	
Fatal	✓	✓		

1. not adjudicated

LT=life threatening, ICH=intracranial hemorrhage, GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries

Overall relative risk of serious bleeding
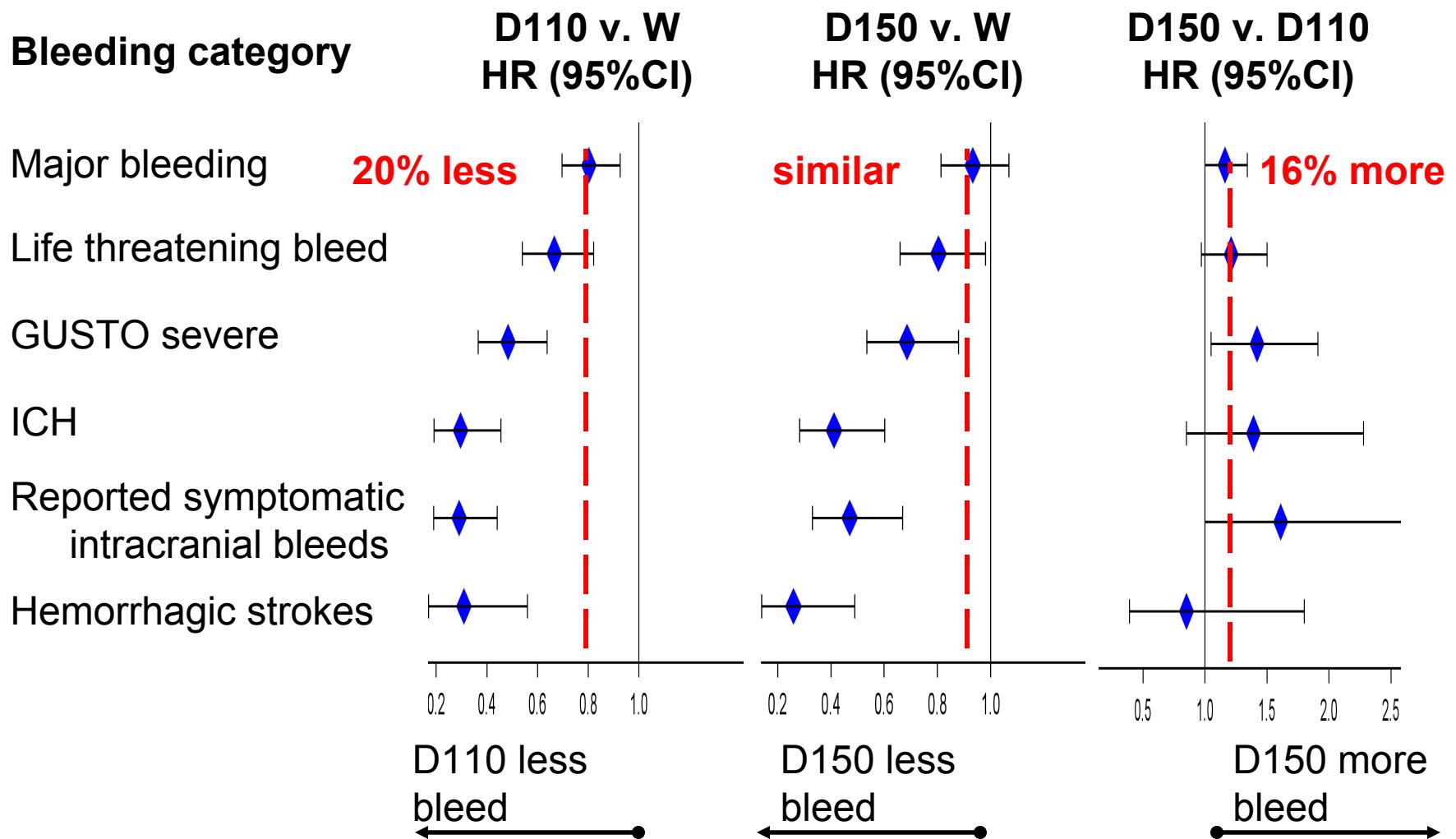
GUSTO severe bleeding in RE-LY

events
W   151
D150   106
D110   74

	HR	95% CI
D110 v W	0.48	(0.36, 0.63)
D150 v W	0.68	(0.53, 0.88)
D150 v. D110	1.42	(1.05, 1.91)

annual rate
1.3%
0.9%
0.6%

No. at risk

D110	6015	5802	5653	4557	3102	1422	81
D150	6076	5836	5672	4603	3162	1442	88
W	6022	5767	5595	4478	2987	1306	72
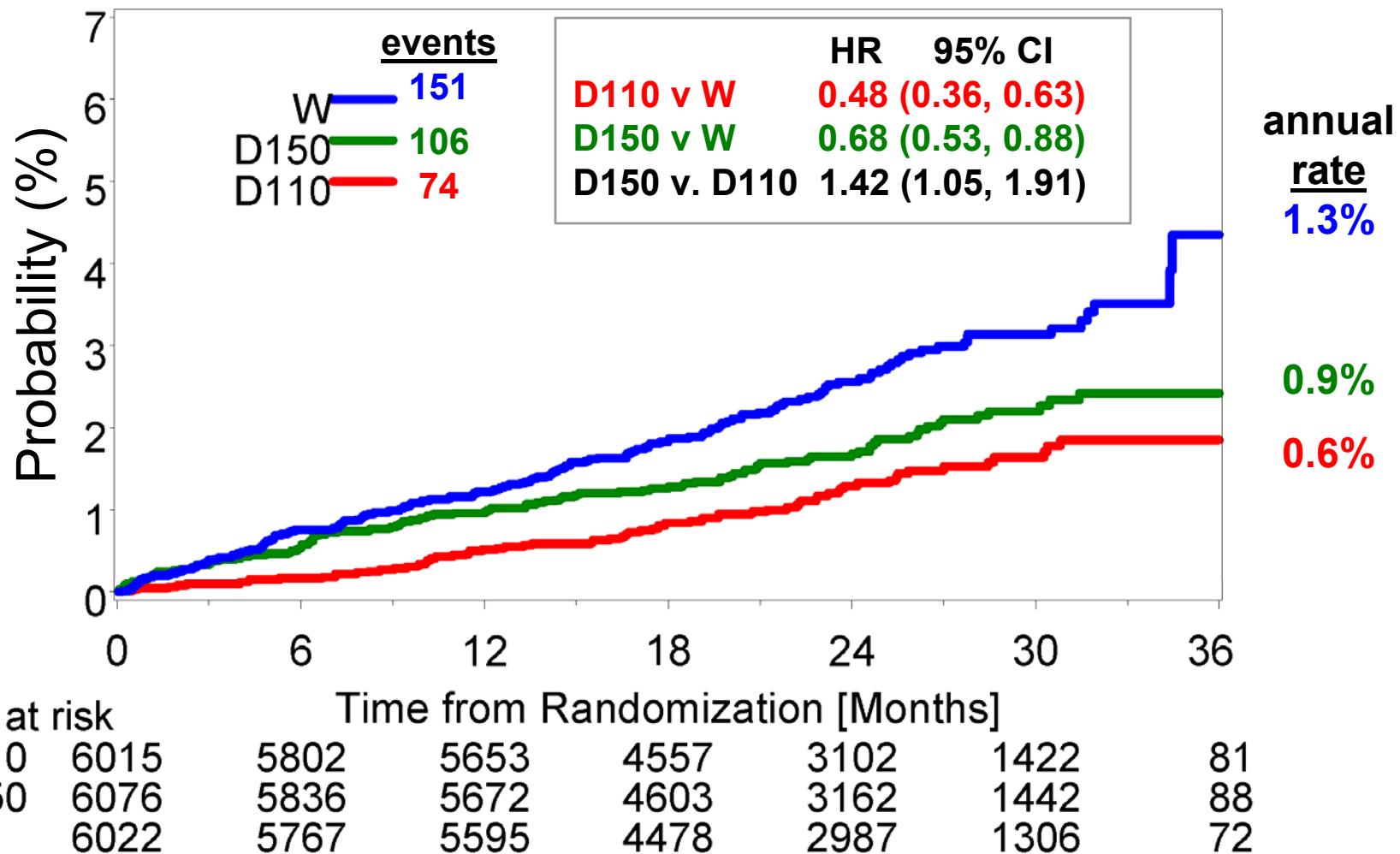
Risk of major bleeding as a function of individual time in therapeutic range (iTTR)

Dabigatran 110 mg vs. Warfarin   **HR (95% CI)**

iTTR < 65% (worse control)

iTTR ≥ 65% (better control)
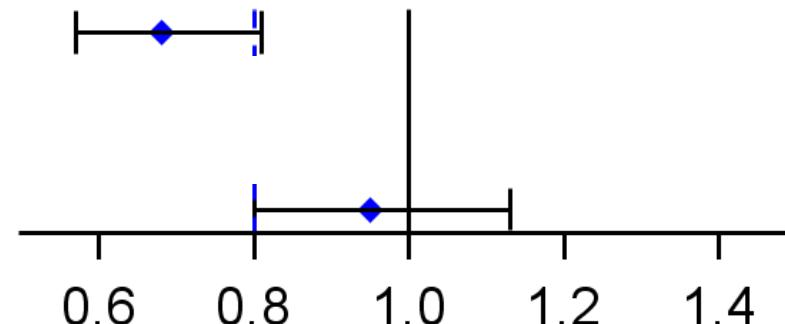
Dabigatran 150 mg vs. Warfarin

iTTR < 65% (worse control)
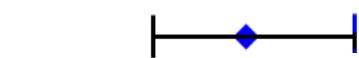
iTTR ≥ 65% (better control)
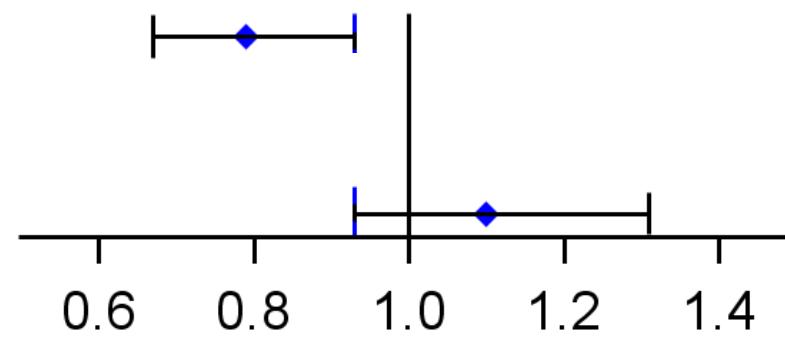
Warfarin more bleeding   Dabi more bleeding

Blue dashed line indicates hazard ratio for overall analysis

Mortality/serious morbidity following major bleeds

- ~25% of all major bleeds did not result in hospitalizations

	Major Bleed n=1378	D150 N=6076
Subject years	2,239	12,033
Annual event rate **(for major bleed, events are 30 days after bleed)**		
All cause death	6.7%	3.6%
Stroke or systemic embolic event Disabling stroke	4.0% 2.0%	1.1% 0.6%
Myocardial infarction	1.1%	0.7 %

- Morbidity and mortality rate higher following a major bleed, but unable to know if bleed led to event

Conclusions on major bleeding

- Dose response for dabigatran

- Bleeding is less on dabigatran 110 mg compared to warfarin irrespective of the definition

- Bleeding is similar on dabigatran 150 mg compared to warfarin, but is less for other serious definitions

- Risk of bleeding on dabigatran similar to warfarin in subjects with more time in therapeutic range

- Risk of bleeding on warfarin driven by subjects with less time in therapeutic range

Analyses of potential
drug induced liver injury (DILI)

Abnormal liver test results in randomized subjects
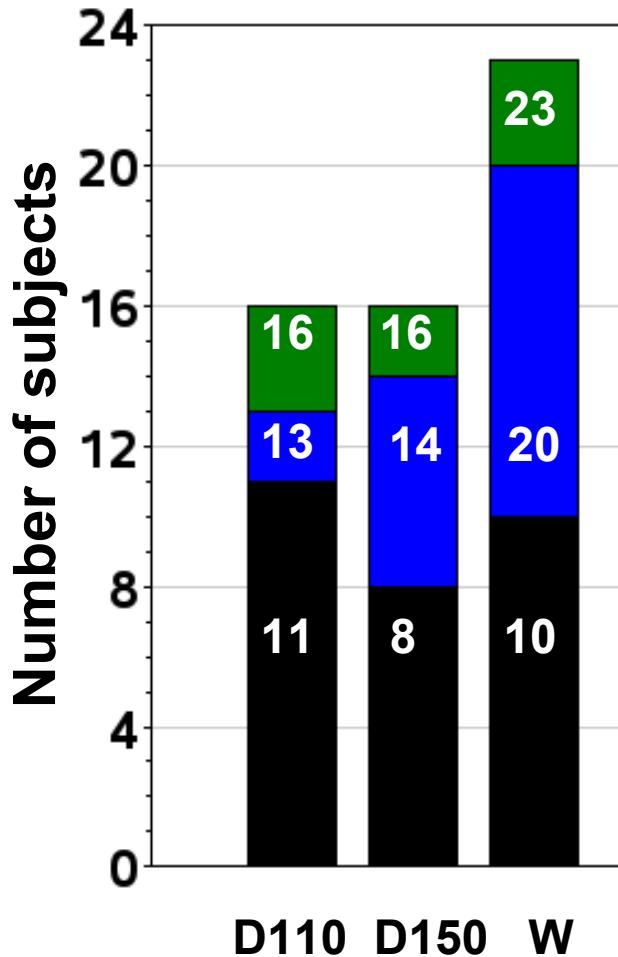
Aminotransferases >3x ULN
& total bilirubin >2x ULN
(not necessarily concurrent)

Aminotransferases >3x ULN
& total bilirubin >2x ULN
(concurrent*)

Potential Hy's
Aminotransferases >3x ULN
& total bilirubin >2x ULN
& alkaline phosphatase <2x ULN
(all concurrent*)

*≤ 30 days after peak aminotransferases (ALT or AST)

Important results of review of 55 cases of interest

- Dr. John Senior and Dr. Leonard Seeff evaluated and scored all 55 cases for clinical severity and probable cause

- Only one subject (D150) had the highest severity score (fatal or requiring liver transplantation due to liver failure); however, causality of DILI was unlikely

- One "probable" case of DILI (D110)
  - DILI more likely than all other causes combined; only one other possible cause (heart failure)

- No "very likely" or "definite" cases of DILI

Warfarin cases of interest

- Cases of interest in the warfarin treatment arm of RE-LY were ~6.5-fold greater than that seen in SPORTIF V, a similar trial comparing ximelagatran to warfarin
  - 23 cases in 6022 subjects in RE-LY vs. 1 case in 1922 subjects in SPORTIF V

- The reason for this difference is not clear
  - Frequency of monitoring of liver tests similar
  - Background diseases similar (40% with heart failure in SPORTIF V versus 32% in RE-LY)
  - Longer duration of RE-LY?
    - 12,000 subject years per arm vs. 6400 total in SPORTIF V
  - Geographic differences?

- All warfarin cases had other probable cause (e.g., heart failure, shock, biliary stones)

Conclusions on dabigatran drug induced liver injury

- Randomized, controlled, clinical data support a low potential for serious DILI

- Recommend no routine liver monitoring

- Investigate patients with symptoms of possible liver dysfunction or abnormal liver tests to determine the probable cause

Analysis of myocardial infarction

Risk of myocardial infarction

	events		HR	95% CI
D150	89	D110 v W	1.30	(0.95, 1.80)
D110	87	D150 v W	1.32	(0.96, 1.81)
W	66			

annual rate

- 0.7%
- 0.7%
- 0.5%

Probability (%)

Time from Randomization [Months]

No. at risk						
D110	6015	5884	5747	4657	3170	1466
D150	6076	5941	5802	4718	3237	1489
W	6022	5896	5760	4651	3108	1376
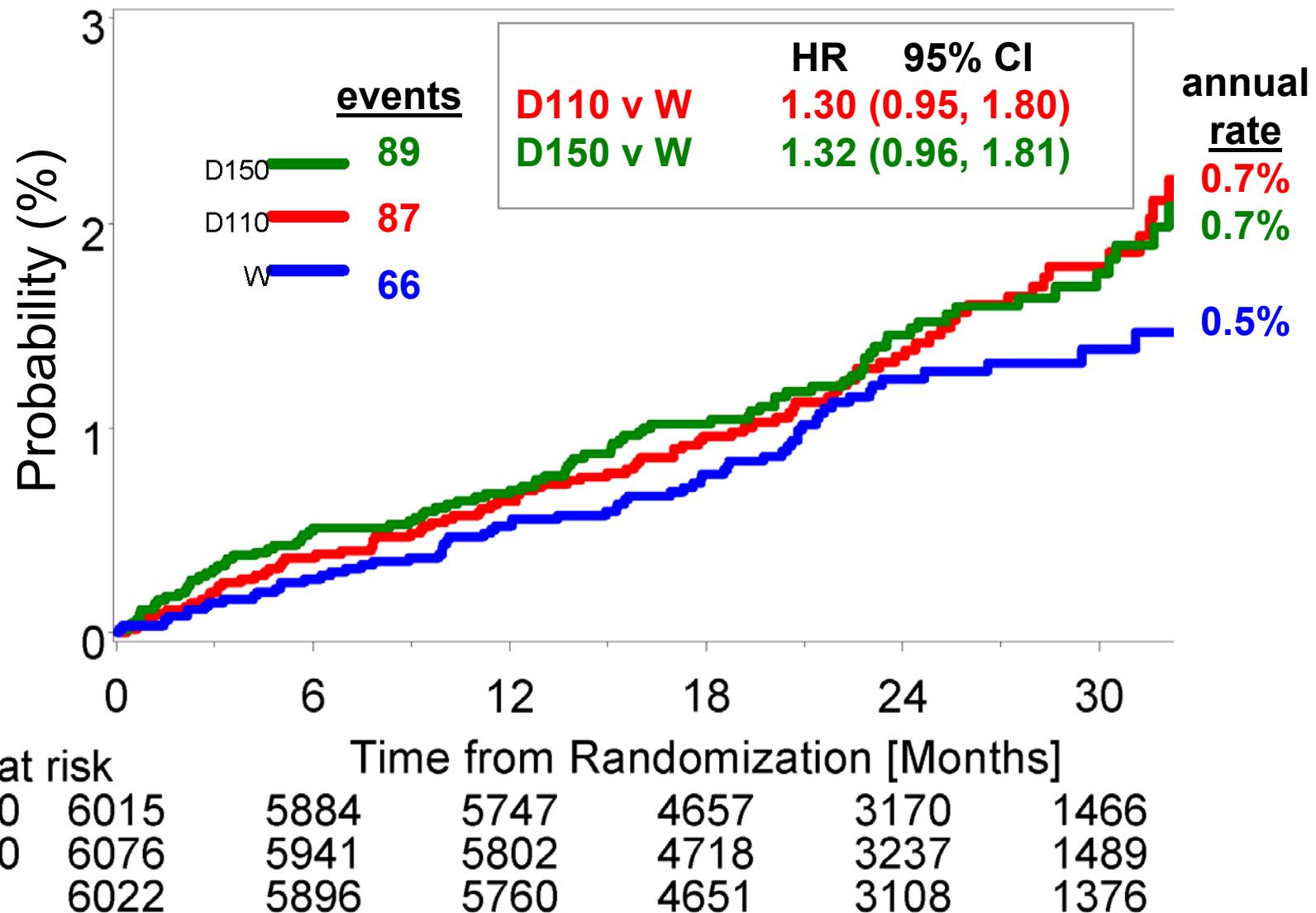
Imbalance in myocardial infarction

	D110		D150		W	
	n	%	n	%	N	%
Total randomized	**6015**	**(100)**	**6076**	**(100)**	**6022**	**(100)**
First MI	**87**	**(1.4)**	**89**	**(1.5)**	**66**	**(1.1)**
MI on drug	**56**	**(0.9)**	**59**	**(1.0)**	**46**	**(0.8)**
MI $\leq$ 6 days off	**13**	**(0.2)**	**10**	**(0.2)**	**8**	**(0.1)**
MI $\leq$ 30 days off	**15**	**(0.2)**	**13**	**(0.2)**	**12**	**(0.2)**
MI > 30 days off	**15**	**(0.2)**	**17**	**(0.3)**	**8**	**(0.1)**

source: adapted from sponsor's table 15.2.5:15

- Numerical imbalance in clinical myocardial infarction persisted off treatment

Assessment of myocardial infarction

- No clear difference in baseline characteristics between treatment groups that might explain imbalance in MIs

  – Reasonably similar with respect to hypertension, diabetes, coronary artery disease, prior MI, age, cholesterol, and concomitant medications

- MACE event rate does not raise concern

  – D110 3.4%, D150 2.8%, W 3.4%

- Risk relative to warfarin was not statistically significant

- If this is a real drug related adverse event, then the trend shows that treating 1000 subjects with dabigatran for one year will cause 2 excess MIs compared to treating with warfarin

- The possible risk of MI should be weighed with the proven benefits of stroke reduction

# NDA 22-512 Dabigatran

Net Benefit Analyses

Cardio-Renal Advisory Committee Meeting

September 20, 2010

Nhi Beasley, Pharm.D. and Aliza Thompson, M.D., M.S.

# Summary of efficacy and safety relative to warfarin in RE-LY

- Dose response demonstrated on stroke and systemic embolic events (SEE) and major bleeding

	D110 mg	D150 mg
Stroke, SEE	⟷	⬇
Major bleeding	⬇	⟷
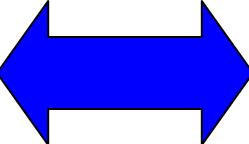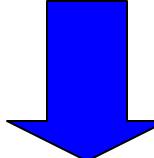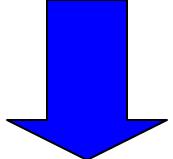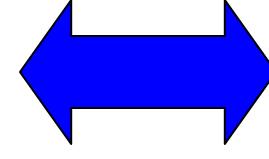
Exploratory net benefit analyses

- Analysis problematic because a method is needed to adjust for the clinical import of events

- Reasons for analysis

  - Understanding the relationship between risk and benefit is important to both regulatory decision making as well as clinical practice

  - Attempt to bring together safety and efficacy findings to support a conclusion about the relative benefit of each dose

  - Weight given to events is important for development programs for stroke prevention in general (deciding which dose(s) to carry into Phase 3)

- We do not believe that these types of composite endpoints should replace usual primary or secondary endpoints in stroke prevention programs

Net benefit analyses equally weighting bleed with stroke does not strongly favor one dose

Annual rate

Time to first event of	HR (95% CI)	D110	D150
ICH, stroke, SEE		1.6	1.3
GUSTO severe, disabling, fatal stroke		1.4	1.4
Life threatening bleed, stroke, SEE		2.5	2.4
Major bleed, stroke, SEE		4.1	4.1

0.6   0.8   1.0   1.2

D150 Better   D110 Better
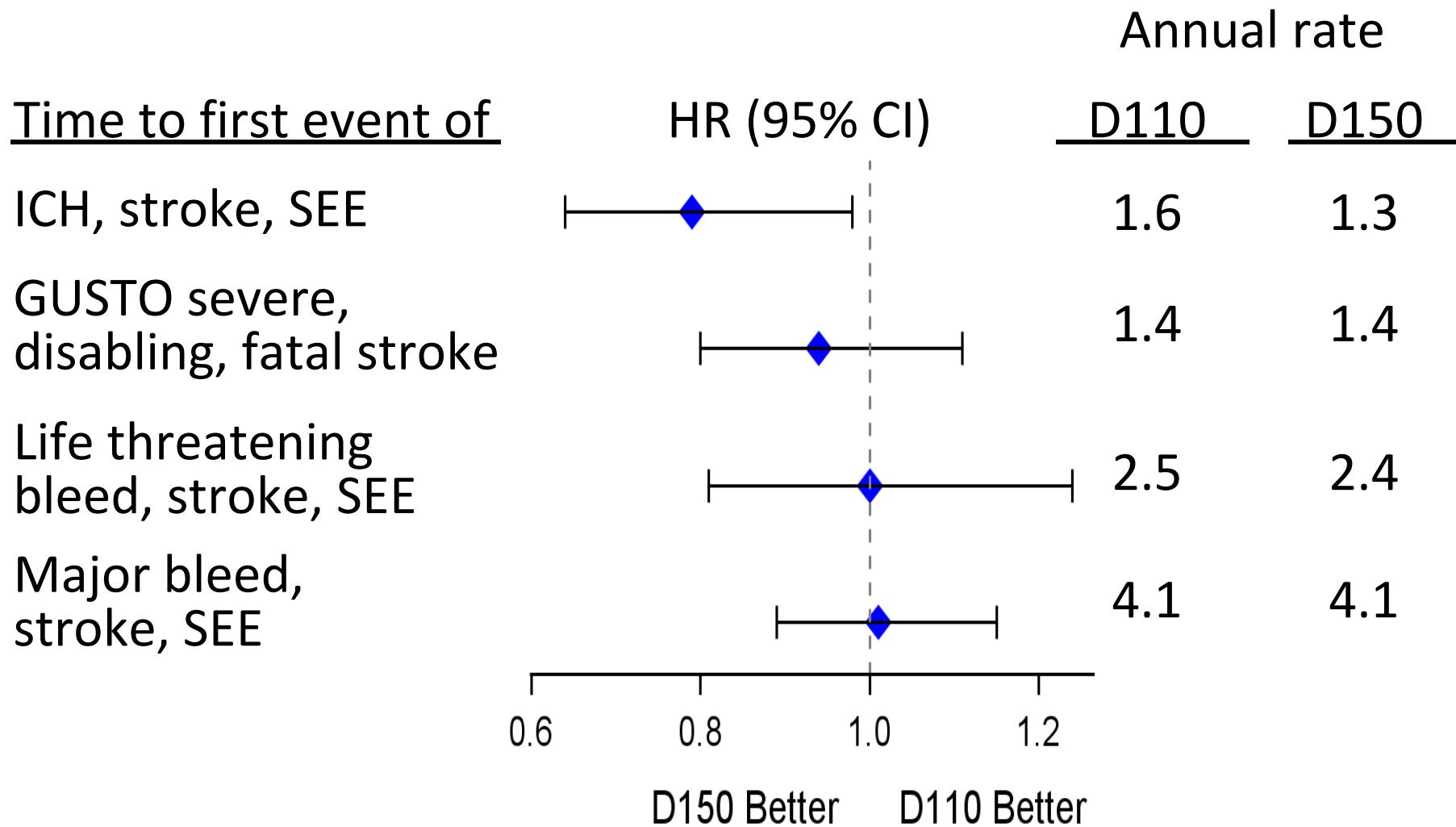
Annual event rates

Event	D110 (n=6015)		D150 (n=6076)	
	events	%/yr	events	%/yr
Life threatening bleed	147	1.2	179	1.5
GUSTO severe	74	0.6	106	0.9
ICH	27	0.2	38	0.3
Stroke/SEE	183	1.5	134	1.1
Stroke	171	1.4	122	1.0
Ischemic stroke	152	1.3	103	0.9
Ischemic stroke or type uncertain	159	1.4	111	0.9
Disabling/fatal strokes	103	0.9	76	0.6
Disabling /fatal strokes excluding hemorrhagic	92	0.8	66	0.6

Elderly (≥ 75 years old) net benefit analyses equally weighting bleed with stroke

Time to first event of	HR (95% CI)	Annual rate D110	Annual rate D150
ICH, stroke, SEE		2.0	1.7
GUSTO severe, disabling, fatal stroke		2.1	2.0
Life threatening bleed, stroke, SEE		3.4	3.4
Major bleed, stroke, SEE		5.7	6.1

0.6   0.8   1.0   1.2

D150 Better   D110 Better
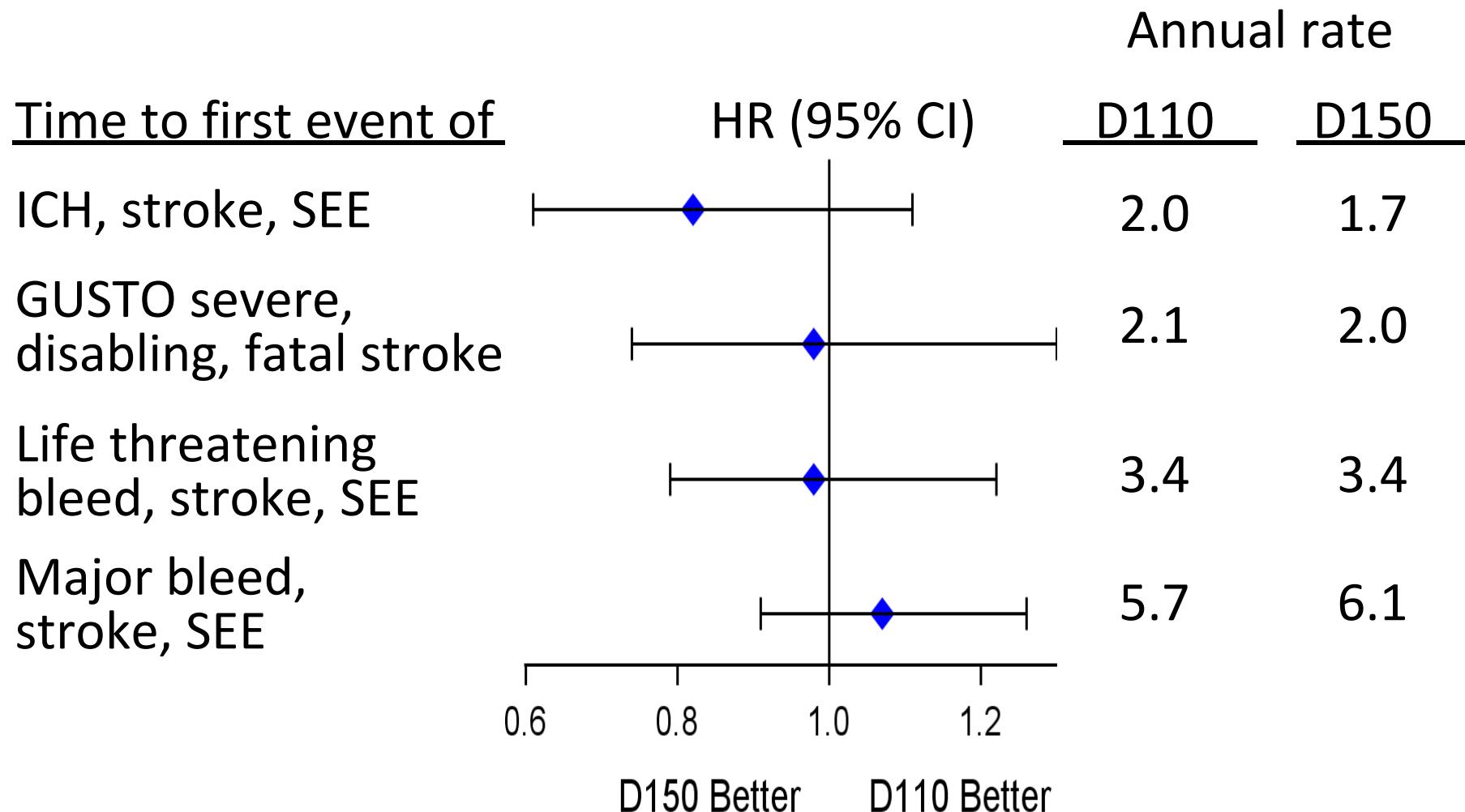
Conclusions on net benefit analyses

- Annual rates of combined events tended to be lower on dabigatran 150 mg

- Annual rates of individual events suggest that there is a greater reduction in strokes compared to the increase in bleeds as you move from D110 to D150

- The appropriate balance between reduction in stroke risk and increase in bleeding risk depends on the clinical import of each

- While the elderly are at higher risk for bleeding, these analyses suggest that there is no clear advantage for dabigatran 110 mg dose

U.S. Food and Drug Administration
Protecting and Promoting Public Health

Exposure Response Analysis of Dabigatran in RE-LY

Kevin M. Krudys, Ph.D.

Division of Pharmacometrics

Office of Clinical Pharmacology

September 20, 2010

Relevant Advisory Committee Questions

1.2 Were reasonable doses selected for study in RE-LY?

6.5 Which, if any, dose(s) of dabigatran should be approved to be marketed in the USA?

6.6 Has the dose-response relationship for dabigatran been adequately defined? If not, what doses would you like to see in a future study?

Key Points to be Addressed

- Assess the need for studying dabigatran at higher doses based on exposure-response

- Assess the need for 110 mg dose for elderly patients

Value of Exposure-Response Analysis

- Concentrations of drugs drive the effect (in general)

- Contributes to evidence of effectiveness

- Provides an efficient approach to select doses to be studied in trials and for labeling, even from fixed doses due to PK variability

- Allows for deriving optimal doses in general and in special populations

Exposure-Response Guidance. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf
Dose Response Guidance. http://www.ich.org/LOB/media/MEDIA480.pdf

Exposure-Response Analysis

- Data
  - Steady-state dabigatran concentrations obtained in 8441 subjects receiving dabigatran (110 and 150 mg) at Month 1 visit
  - Time to first event while on study medication
- Analysis
  - Time to event analysis accounted for exposure and other relevant risk factors (demographics, medical history, etc.)
  - Effectiveness
    - Ischemic Stroke
  - Safety
   - Life-Threatening Bleed

Does Benefit/Risk Support Exploration of Higher Doses of Dabigatran?
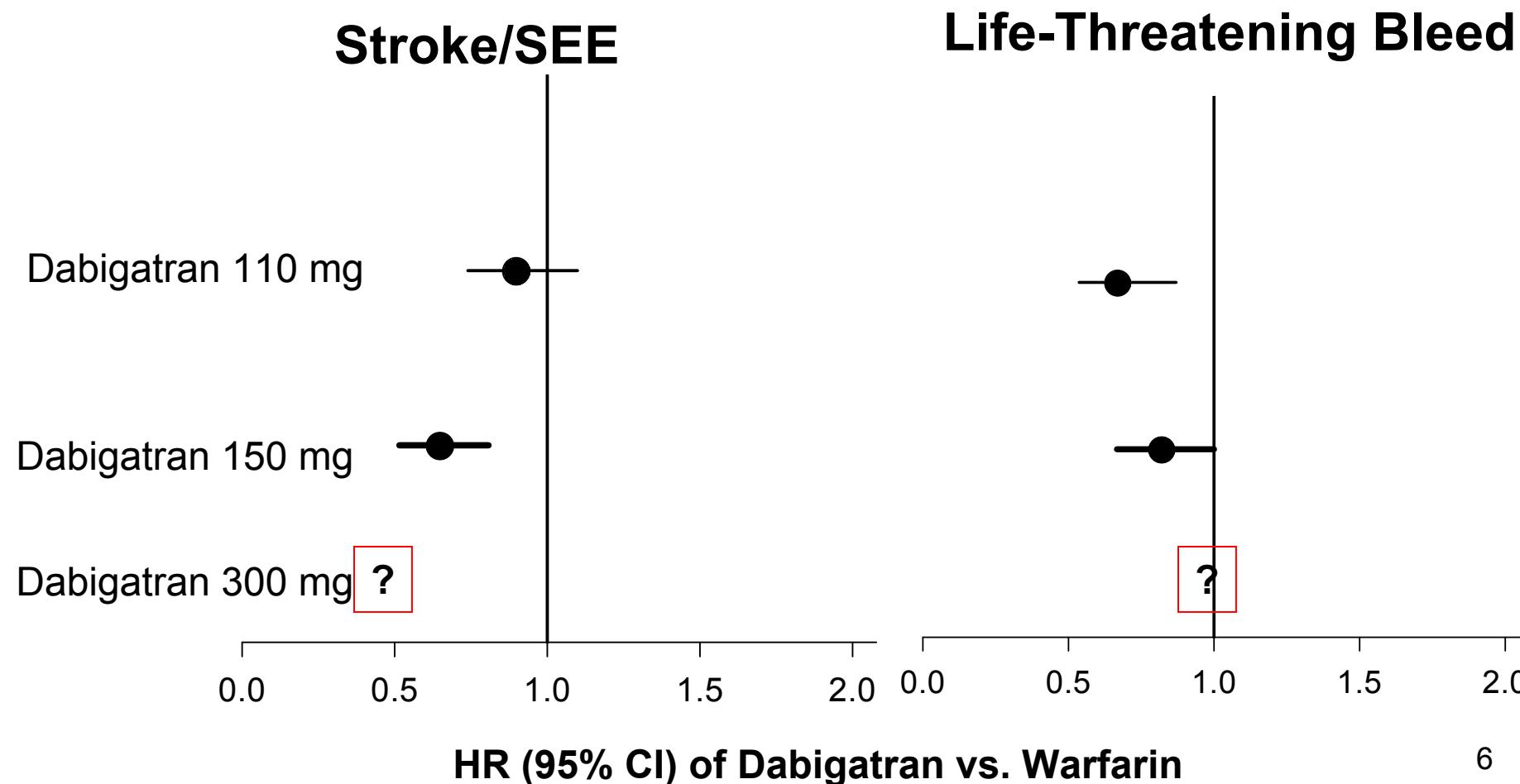
Increase in Dabigatran Concentration Reduces Probability of Ischemic Stroke

Additional risk factors: Age, weight, history of stroke/TIA, diabetes
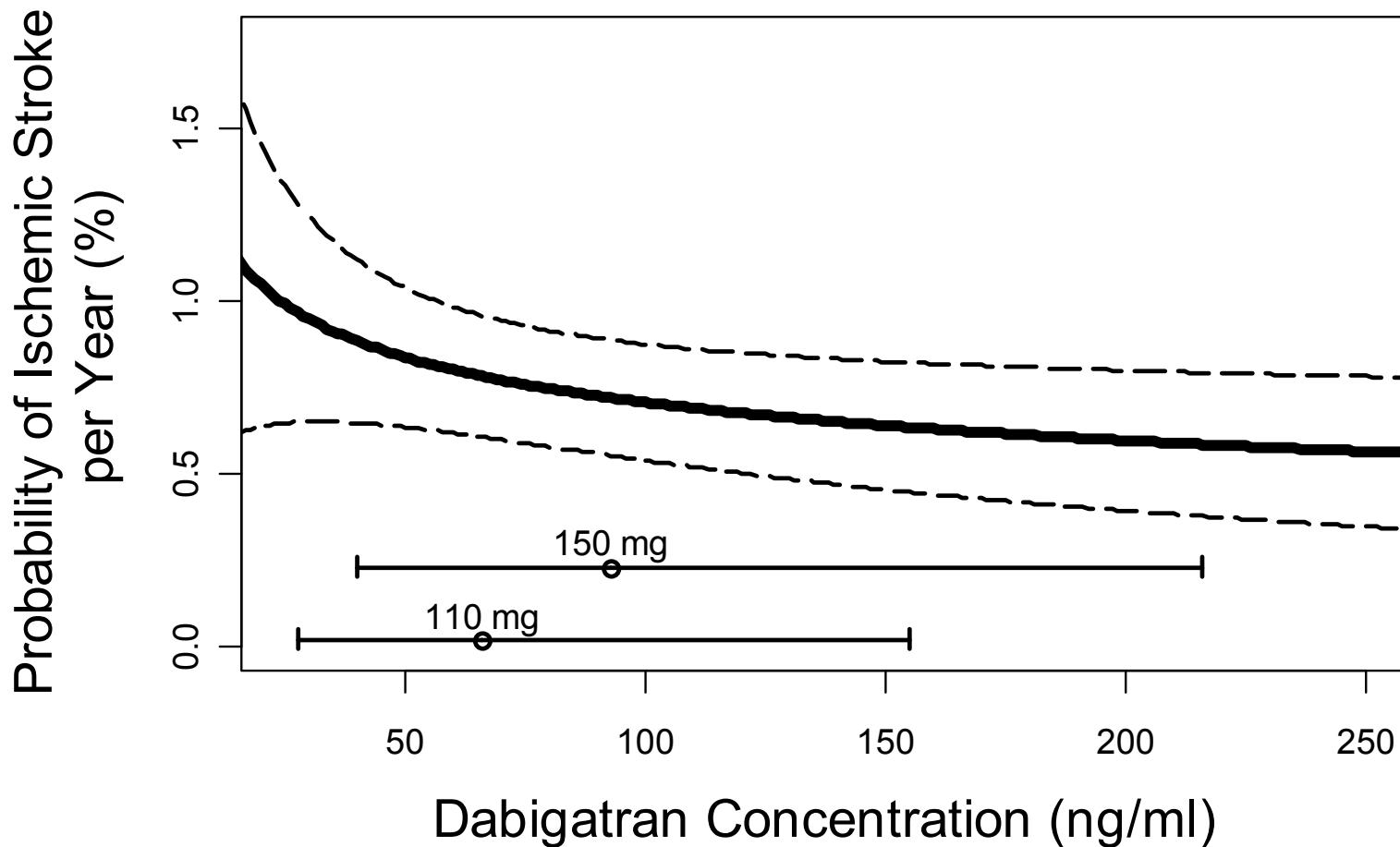
Increase in Dabigatran Concentration Increases Probability of Life-Threatening Bleed

Additional risk factors: Age, sex, history of stroke/TIA, coronary artery disease
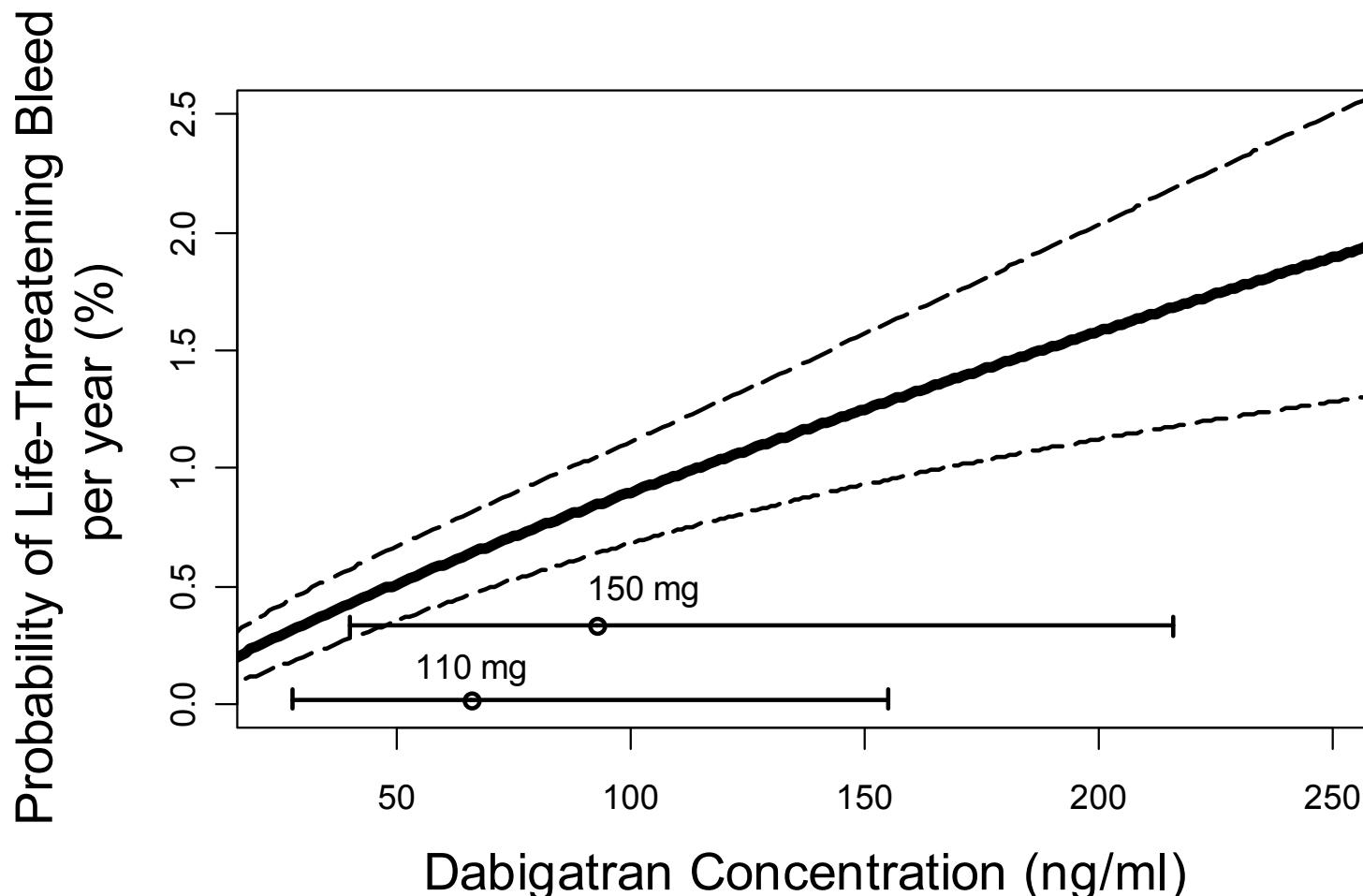
Does Benefit/Risk Support Exploration of Higher Doses of Dabigatran?

Key Points to be Addressed

- Assess the need for studying dabigatran at higher doses based on exposure-response

- Assess the need for 110 mg dose for elderly patients

Impact of Age on Benefit/Risk
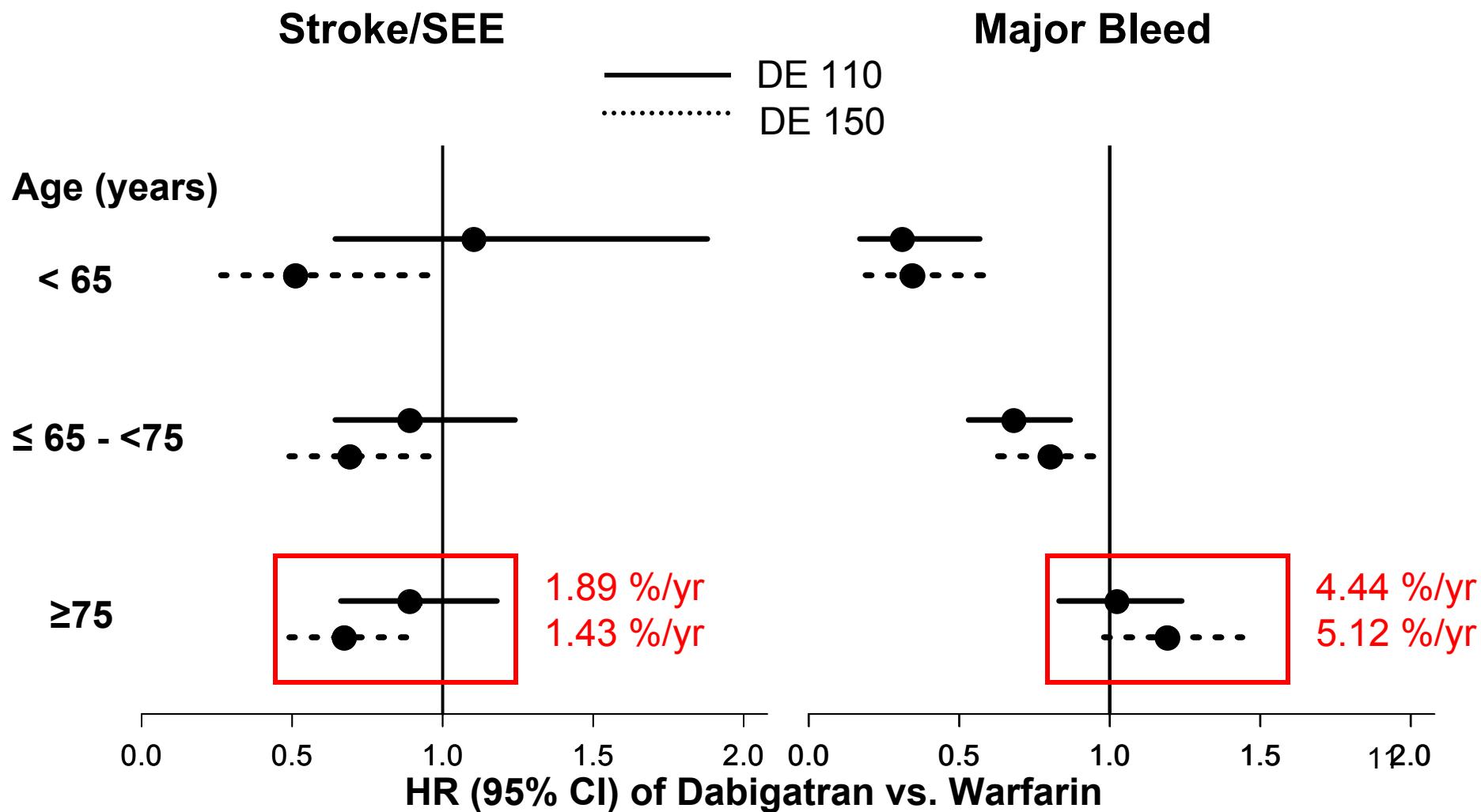
Dabigatran Concentrations are Inversely Related to Renal Function

12
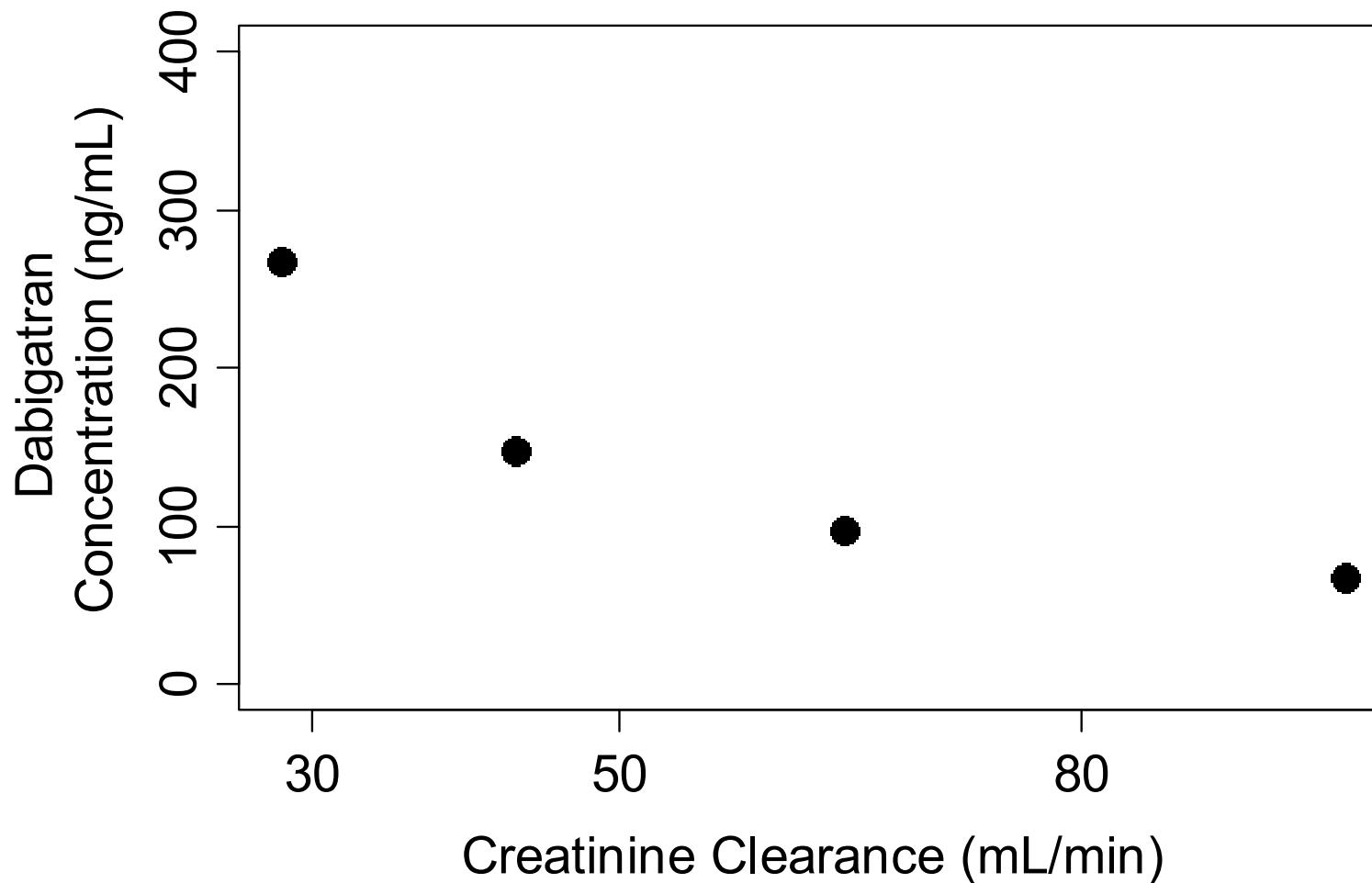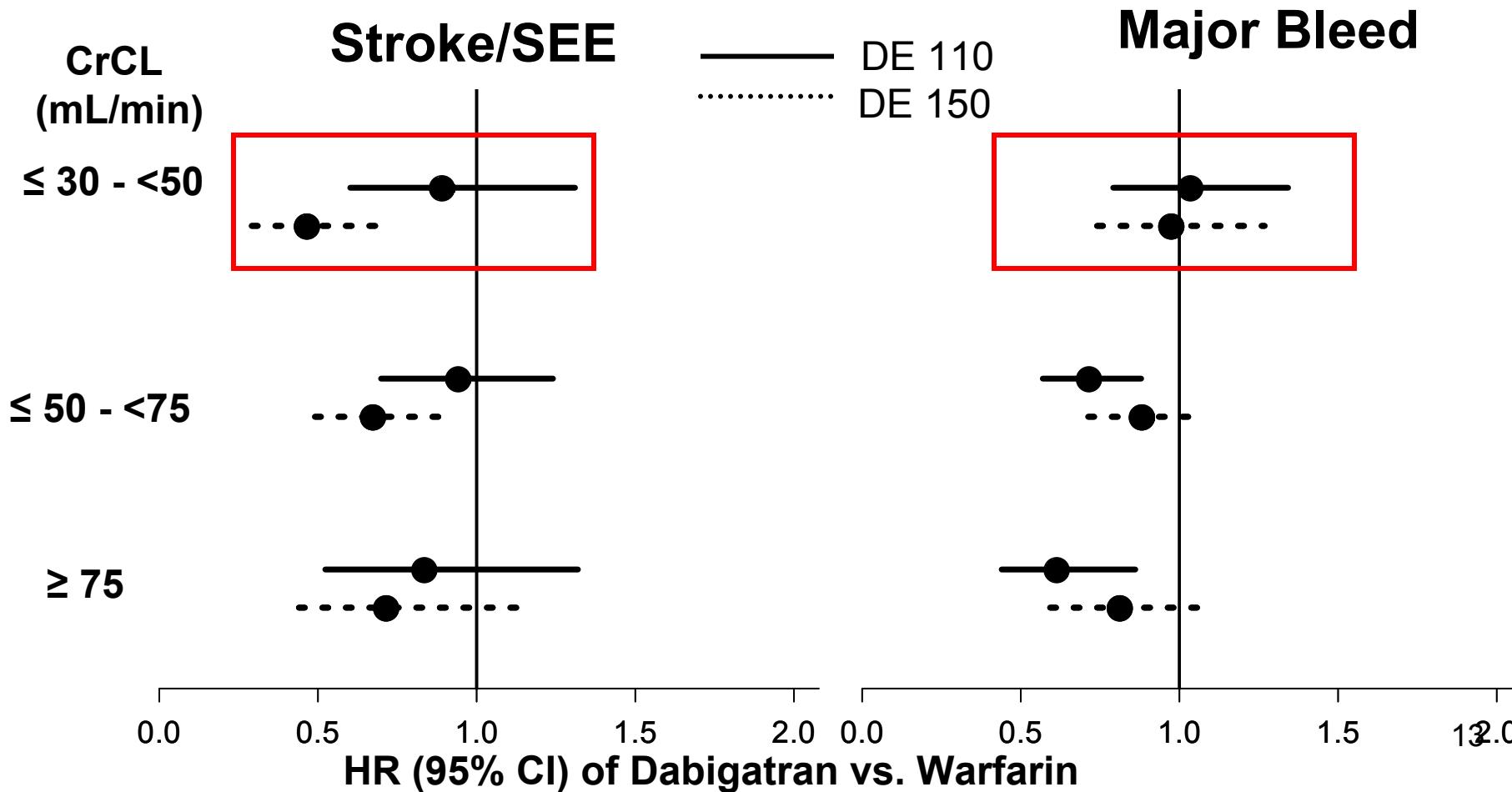
Conclusions

- Higher dabigatran concentrations result in lower probability of ischemic stroke

- Higher dabigatran concentrations result in higher probability of life-threatening bleed

- Value of higher doses depends on how one weights bleeding events vs. strokes

- Lower dose (110 mg) in elderly patients could compromise effectiveness, without obvious advantage for major bleed

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